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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JO KLAVENESS, EDWIN JOHANNESEN, and HELGE TOLLESHAUG

Appeal 2009-0453
Application 10/573,606
Technology Center 1600

Decided:[1] March 26, 2009

Before DEMETRA J. MILLS, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims 13, 15-18, and 20-24, which are directed to an imaging contrast agent. The Examiner

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

Claim 13 is representative of the claims on appeal and reads as follows:

Claim 13: An optical imaging contrast agent with affinity for an abnormally expressed biological target associated with colorectal cancer (CRC), said contrast agent being of formula I:

V-L-R (I)

wherein:

V is one or more vector moieties having affinity for an abnormally expressed target in CRC, where said target is selected from c-met, MMP-14, COX-2, beta-catenin and cathepsin B;

L is a linker moiety or a bond, and

R is one or more reporter moieties detectable in optical imaging, wherein the contrast agent has a molecular weight below 10,000 Daltons.

The claims stand rejected under 35 U.S.C. § 103(a) as follows:

- claims 13, 15-18, and 20-24 in view of Marten,[2] Klaveness,[3] and Waggoner,[4] and
- claims 13, 15-18, and 20-24 in view of Weissleder,[5] Klaveness, and Waggoner.

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[2] Marten et al., *Detection of Dysplastic Intestinal Adenomas Using Enzyme-Sensing Molecular Beacons in Mice,* 122 GASTROENTEROLOGY 406-414 (2002).

[3] Klaveness et al., US 6,610,269 B1, Aug. 26, 2003.

[4] Waggoner et al., US 6,008,373, Dec. 28, 1999.

[5] Weissleder et al., *In vivo imaging of tumors with protease-activated near-infrared fluorescent probes,* 17 NATURE BIOTECHNOLOGY 375-378 (1999).

OBVIOUSNESS I

Issue

The Examiner has rejected claims 13, 15-18, and 20-24 under 35 U.S.C. § 103(a) as being obvious in view of Marten, Klaveness, and Waggoner. Claims 15-18 and 20-24 have not been argued separately and therefore stand or fall with claim 13. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that Marten "discloses cathepsin B sensing … probes comprising Cy5.5 (cyanine dye) containing cleavage sites, … for imaging of the colon" (Office Action mailed Sept. 24, 2007, at 2), Klaveness "discloses contrast agents of formula V-L-R where V is a vector moiety (i.e. peptide or non-peptide), L is a linker moiety … and R is a detectable reporter moiety/moieties (i.e. cyanine dye)" *(id.* at 3), and Waggoner "discloses that low molecular weight fluorescent labeling complexes/probes containing cyanine dyes, linkers and proteins have enhanced cell penetrating capabilities" (*id.*). The Examiner concludes that "it would have been obvious to one ordinarily skilled in the art to minimize the molecular weight of the fluorochrome probes of Maten [sic] et al. to about 500 to 10000 Daltons by minimizing the linker molecular weight or the number of detectable reporter moieties to provide for probes having greater penetration into cellular environments" (*id.* at 4).

Appellants contend that the Examiner erred in finding that the combination of the cited references suggests a contrast agent having "a molecular weight below 10,000 Daltons," as claimed, because modifying the probe of Marten to have such a molecular weight is in direct contradiction to Marten's teaching (Appeal Br. 5).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the cited references would have made obvious to one of skill in the art the claimed probe having "a molecular weight below 10,000 Daltons"?

Findings of Fact

1. Marten discloses that, in a mouse model for familial adenomatous polyposis, "[c]athepsin B was consistently overexpressed in adenomatous polyps" (Marten, abstract).

2. Marten discloses that "[w]hen mice were injected intravenously with the cathepsin reporter probe, intestinal adenomas became highly fluorescent indicative of high cathepsin B enzyme activity" such that "microscopic adenomas were readily detectable by fluorescence, but not light, imaging" (*id.*).

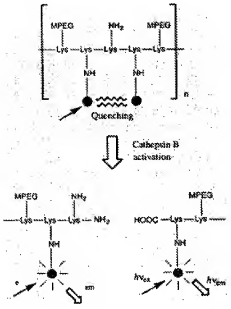
3. Marten discloses that cathepsin B activity can be used as a biomarker to identify adenomas "particularly when contrasted against normal adjacent mucosa" (*id.*).

4. Marten discloses that the cathepsin B reporter probe contained "Cy5.5 monofunctional dye (Amersham Pharmacia Biotech, UK) reporters adjacent to . . K-K . . . cleavage sites on a macromolecular assembly" (*id.* at 408, placeholders in original).

5. Marten discloses that the cathepsin B reporter probe is described in more detail in Weissleder (*id.*) (Weissleder is cited *supra* at footnote 5).

6. Marten discloses that the macromolecular "assembly consisted of a synthetic graft copolymer containing partially pegylated (5 kilodaltons) poly-L-lysine (35 kilodaltons)" (*id.*).

7. Figure 1 of Marten is shown below:



(*Id.* at 408). Figure 1 shows a "[s]chematic diagram of the cathepsin B probe and its activation" (*id.*, legend to Fig. 1).

8. Marten states that "[t]he fluorochromes are essentially nonfluorescent in their native state caused by energy resonance transfer among fluorochromes" (*id.*); in other words, the adjacent fluorochromes "quench" each other. Marten states that, "[o]n enzymatic cleavage the agent becomes fluorescent in the near-infrared" (*id.*), as shown at the bottom of Figure 1.

9. Waggoner discloses "a low molecular weight fluorescent labeling complex which includes a first, or donor, fluorochrome having first absorption and emission spectra, and a second, or acceptor, fluorochrome having second absorption and emission spectra. At least one of the first or second fluorochromes is a cyanine dye." (Waggoner, col. 2, ll. 37-42.)

10. Waggoner discloses that the "complex also includes a linker for covalently attaching the fluorochromes to permit resonance energy transfer between the first and the second fluorochromes" (*id.* at col. 2, ll. 50-52).

11. Waggoner discloses that the "fluorescent labeling complexes of the invention have low molecular weights and can be readily conjugated to antibodies, other proteins, and DNA probes" (*id.* at col. 6, ll. 12-14).

12. Waggoner discloses "low molecular weight" means that the "molecular weight of the fluorochromes and linker of the complex is between about 500 and 10,000 Daltons, and for a two fluorochrome complex, preferably in the range of 1000 to 2500 Daltons. Therefore, these labeled species will have much greater penetration into intracellular environments than is possible with … large phycobiliprotein labels" (*id.* at col. 6, ll. 15-22).

13. Waggoner discloses that the "low molecular weight fluorescent labeling complexes of the invention should be valuable not only for flow cytometry, but also for laser confocal microscopy and for other detection systems requiring multicolor detection with single wavelength excitation" (*id.* at col. 6, ll. 23-27).

Principles of Law

"In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted).

The obviousness analysis "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, __, 127 S. Ct. 1727, 1741 (2007).

"Two criteria have evolved for determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved." *In re Clay*, 966 F.2d 656, 658-59 (Fed. Cir. 1992).

Analysis

Claim 13 is directed to an imaging contrast agent having the formula V-L-R and a molecular weight below 10,000 Daltons, where V is a vector moiety having affinity for cathepsin B (among other targets), L is a linker moiety or a bond, and R is a reporter moiety that can be detected in optical imaging.

Marten discloses that cathepsin B levels are elevated in colon adenomas and that contrast agents that are activated by cathepsin B enzyme activity are useful for imaging colon adenomas. Waggoner discloses that low molecular weight contrast agents (i.e., with the reporter/linker complex being preferably between 500-10,000 daltons) are useful because they have enhanced cellular penetration. In view of these disclosures, it would have been obvious to one of skill in the art to modify the Marten cathepsin B-targeting agent by reducing the size of the polylysine moiety so that the overall size of the molecule would have a molecular weight below 10,000 daltons. Motivation to do so is provided by Waggoner, which teaches that a

low molecular weight contrast agent has enhanced cellular penetration. The disclosure of Klaveness is cumulative.

Appellants argue that the Marten probe (as evidenced by Weissleder) far exceeds "the molecular weight limit of 10,000 Daltons (10 kDa) of present claim 13" (Appeal Br. 4) and that modification of the probe to meet the claim limitation "is in direct contradiction to the teaching of Marten/ Weissleder" (*id.* at 5) because "those references teach that the high molecular [weight] copolymer is an essential part of a successful strategy for tumor imaging" (*id.* at 6).

This argument is not persuasive. Although the specific complex disclosed by Marten (and by Weissleder) is significantly larger than 10,000 daltons, the size of the complex appears to be designed to increase the persistence of the complex in the bloodstream. *See* Weissleder 375, abstract: "NIRF probes were bound to a long circulating graft copolymer consisting of poly-L-lysine and methoxypoly-ethylene glycol succinate."

Based on the mechanism described by Marten, however, one of skill in the art would recognize that the large size of the complex is not required to assay cathepsin B activity. That is, the signal is generated from the reporter disclosed by Marten when cathepsin B cleaves between two adjacent lysine residues (". . K-K . . ."; Marten 408), which separates the fluorochrome molecules and eliminates quenching (Marten, Fig. 1). Thus, one of skill in the art would reasonably expect that a smaller Cy5.5 probe would also function in assaying for cathepsin B in tumors, while showing enhanced cellular uptake. One of skill in the art would have considered it obvious to use the smaller complex to assay for cathepsin B activity when

enhanced penetration is more advantageous than having a long persistence time in the bloodstream, such as when the complex is administered locally.

Appellants also argue that the description in Waggoner of low molecular weight complexes as "between about 500 and 10,000 Daltons" refers only to the molecular weight of a complex of an attached first and second fluorochrome and not to a complex of the first and second fluorochromes attached to a targeting molecule (Appeal Br. 8-9).

This argument is not persuasive. Although Waggoner's specific teaching of a molecular weight between 500 to 10,000 daltons is in reference to two fluorochromes attached to a linker, one of skill in the art would understand that the small size of the fluorochromes and linker allow a smaller size, and increased cellular uptake, of the complex as a whole. Thus, Waggoner's teaching would have made it obvious to reduce the size of Marten's whole complex, including the targeting portion, in order to facilitate cellular penetration.

Appellants also argue that "Waggoner is not even of the same utility as the present invention, since it is silent on both *in vivo* imaging and contrast agents" (Appeal Br. 9).

This argument is not persuasive. Claim 13 is drawn to a contrast agent that targets cathepsin B, which is an intracellular enzyme. *See* Weissleder 376, left-hand col. (cathepsin B is part of the "endosomal lysosomal system"). Thus, one of skill in the art would understand that the principles of cell penetration that apply in the imaging of isolated cells would apply to imaging of cathepsin B done either *in vitro* or *in vivo*. In either case, the imaging agent must penetrate the cell prior to binding the

intracellular cathepsin B. That is, in accord with *In re Clay*, Waggoner is the same field of endeavor as the present invention.

Conclusions of Law

The evidence of record supports the Examiner's conclusion that the cited references would have made obvious to one of skill in the art the claimed probe having "a molecular weight below 10,000 Daltons."

OBVIOUSNESS II

Issue

The Examiner has rejected claims 13, 15-18, and 20-24 under 35 U.S.C. § 103(a) as being obvious in view of Weissleder, Klaveness, and Waggoner. Claims 15-18 and 20-24 have not been argued separately and therefore stand or fall with claim 13. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that Weissleder discloses "probes for in vivo imaging comprising poly-L-lysine, MPEG [methoxypolyethylene glycol] and Cy5.5 (cyanine dye)" that "are enzymatically activatable" and that "were internalized into colon adenocarcinoma via uptake through fluid phase endocytosis" (Office Action mailed Sept. 24, 2007, at 4-5). The Examiner relies on Waggoner (and Klaveness) as discussed above.

The Examiner concludes that

> it would have been obvious to one ordinarily skilled in the art to minimize the molecular weight of the fluorochrome probes of Weissleder et al. to about 500 to 10000 Daltons by minimizing the linker molecular weight or the number of detectable reporter moieties to provide for probes having greater penetration into cellular environments.

(*Id.* at 6.)

Appellants contend that the Examiner erred in finding that the combination the cited references suggests a contrast agent having the claim limitation of "a molecular weight below 10,000 Daltons" because modifying the probe of Weissleder to have such a molecular weight is in direct contradiction to the teaching of Weissleder (Appeal Br. 5).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the cited references would have made obvious to one of skill in the art the claimed probe having "a molecular weight below 10,000 Daltons?"

Additional Findings of Fact

14. Weissleder discloses the use of near-infrared fluorescence (NIRF) probes to image tumor-associated lysosomal activity in a mouse model (Weissleder, abstract).

15. Weissleder discloses that the probe was

> a synthetic graft copolymer consisting of poly-L-lysine (PL) sterically protected by multiple methoxypolyethylene glycol (MPEG) side chains as a delivery vehicle of quenched fluorochromes to tumors. ... Each PL backbone contained an average of 92 MPEG molecules and 11 molecules of Cy5.5 yielding $(Cy5.5)_{11}$-PL-$MPEG_{92}$. ... The molecule contains 44 unmodified lysines on the backbone as sites for cleavage by enzymes with lysine-lysine specificity.

(*Id.* at 375.)

16. Weissleder discloses that the graft copolymer had an average molecular weight of 480 kDa prior to modification with the Cy5.5 dye (*id.* at 377).

17. Weissleder discloses that "[t]umoral delivery of the quenched NIRF probes is facilitated by a novel, long, circulating [sic, long-circulating], synthetic graft copolymer" (*id.* at 375).

18. Weissleder discloses that the "copolymer accumulates in tumors by slow leakage across highly permeable neovasculature" (*id.*).

19. Weissleder discloses that "[i]nternalization of the copolymer into tumor cells occurs by fluid-phase endocytosis" (*id.*).

20. Weissleder discloses that "cysteine protease (cathepsin B, H, and L) inhibitors such as E64 … and leupeptin completely inhibited NIRF generation" and that "trypsin inhibitors … and [a] trypsin-like serine protease inhibitor … inhibited NIRF generation. … [T]hese studies are consistent with NIRF signal generation as a result of lysosomal cysteine/serine protease activity" (*id.* at 376).

Analysis

Claim 13 is discussed above. Weissleder discloses the same contrast agent disclosed by Marten. Weissleder also discloses that the contrast agent is useful for imaging tumors. Waggoner discloses that low molecular weight contrast agents (i.e., with the reporter/linker complex preferably between 500-10,000 daltons) are useful because they have enhanced cellular penetration. In view of these disclosures, it would have been obvious to one of skill in the art to modify the Weissleder cathepsin B-targeting agent by reducing the size of the polylysine moiety so that the overall size of the molecule would have a molecular weight below 10,000 daltons. Motivation to do so is provided by Waggoner, which teaches that a contrast agent with a

molecular weight below 10,000 daltons has enhanced cellular penetration. The disclosure of Klaveness is cumulative.

Appellants' arguments with regard to the rejection of claim 13 in view of the combination of Weissleder, Waggoner, and Klaveness are the same as discussed above for the rejection based on Marten, Waggoner, and Klaveness. These arguments are not persuasive for the reasons set forth above.

Conclusions of Law

The evidence of record supports the Examiner's conclusion that the cited references would have made obvious to one of skill in the art the claimed probe having "a molecular weight below 10,000 Daltons."

SUMMARY

We affirm the rejection under 35 U.S.C. § 103(a) of claims 13, 15-18, and 20-24 in view of Marten, Klaveness, and Waggoner and of claims 13, 15-18, and 20-24 in view of Weissleder, Klaveness, and Waggoner.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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